

Zoran Todorović
Dragana Protić
Department of Pharmacology, Clinical Pharmacology & Toxicology
Faculty of Medicine
University of Belgrade

Bioethical Issues in the Development of Biopharmaceuticals

Abstract: *Development of biopharmaceuticals is a challenging issue in bioethics. Unlike conventional, small molecular weight drugs, biopharmaceuticals are proteins derived from DNA technology and hybrid techniques with complex three dimensional structures. Immunogenicity of biopharmaceuticals should always be tested in clinical settings due to low predictive value of preclinical animal models. However, non-human primates (NHP) and transgenic mice could be used to address certain aspects of immunogenicity. Substantial efforts have been made to reduce NHP use in biopharmaceutical drug development, e.g. study design improvements and changes in regulatory policy. In addition, several expert groups are active in this field (e.g. NC3Rs, BioSafe, and Biopharmaceutical Technical Group). Despite that, there is an increasing trend of use of NHP in preclinical safety testing of biopharmaceuticals, especially regarding monoclonal antibodies. Other potential bioethical issues related biopharmaceutical drug development are their cost/effectiveness ratio, clinical safety assessment, production of biosimilars, and comparison of their efficacy with placebo in countries without intention to market. Identification of the human genome has opened many new bioethical issues. Development of biopharmaceuticals is an important bioethical issue for several reasons. It connects all aspects of contemporary bioethics: biomedicine (e.g. clinical trials in vulnerable subjects), animal welfare and the most recent advances in biotechnology. In particular, biopharmaceutical drug development is a challenging issue regarding treatment of rare diseases.*

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Key words: *bioethics, biopharmaceutics, drug development, immunogenicity, animal welfare, non-human primates.*

1. Introduction

According to a widely accepted definition, bioethics is the philosophical study of the ethical controversies brought about by advances in biology and medicine, for example the Human Genome Project and recent door opening to biosimilars in the EU and US. The concept of integrative bioethics offers us a vision of human scientific and technological development more humane than what occurs in Borislav Pekić's novel "1999"¹.

1 The novel describes search for humanness that had disappeared from Earth long ago ("solitude is genetically inherited").

According to Tom Beauchamp, contemporary bioethics has both theoretical and practical background (Beauchamp 2004: 209). The first corresponds to the philosophical ethical theory, and the other is closer to the problems that are encountered in medical practice. At the same time, Beauchamp predicted a “divorce” between the two approaches. Fortunately, he was wrong at least due to the emerging challenges in biomedical practice. Recent advances in medicine and biology have opened the Pandora’s box and brought numerous controversial issues that require a pluriperspective approach, inherent to integrated bioethics².

2. Bioethics, corporate ethics and biopharmaceuticals

50 There are various bioethical issues related to the production of biopharmaceuticals (biotech drugs), their testing and use. In general, management of pharmaceutical companies is willing to actively promote/support ethical aspects of drug development and use because lapses in corporate ethical conduct lead to inevitable loss of public trust (Eaton 2007: 39). (Bio)ethics is tightly interconnected with drug development processes due to the intrinsic nature of drug products (life/death; health/disability), and because drugs are studied both on animals and humans. There are several aspects of ethics in pharmaceutical industry: business ethics, ethical social behavior and ethical drug development (Fournel 2005: 33). The first aspect involves, for example, commercial activities, contracts, pricing, incentives and kickbacks. At this level, there are different control mechanisms (at least self-regulation, legislation and consumer advocacy) that would mitigate unethical conduct of a business. However, unethical behavior of pharmaceutical companies may involve more subtle mechanism, for example insufficient openness of information sharing, and risk mitigation for patients. Finally, there is a wide spectrum of bioethical issues across the drug development continuum: use of patients in countries without intention to market, inadequate trial design, different safety standards etc.

Access to medicine is a human right as part of the right to health. It was established as a social right in the WHO Constitution (1946), and in the Universal Declaration of Human Rights (1948) by the World Health Organization. Rational drug therapy involves the assessment of a drug’s efficacy, safety, quality and cost (Todorović 2012a: 28). Biopharmaceuticals are often highly effective in the treatment of serious disorders accompanied with high mortality and/or chronic disability. However, their safety is usually confirmed in a limited number of animal models and a small number of patients. Long patent protection prevents other

2 Contemporary bioethics has evolved through different phases, from a social movement focused on practical medical problems and principlism of the 1970s and 1980s to its current integrated concept and pluriperspectivism.

manufacturers to make cheaper copies of these drugs³. In developing countries, the problem of the availability of biopharmaceuticals is due to several factors: their cost, patent protection, regulatory constraints and scientific and technological capacity (Scherer 2011).

Biological therapeutics (vaccines, blood derivatives, biotech drugs/biopharmaceuticals, and other products extracted from native, non-engineered biological sources) are large molecules that differ substantially from the conventional chemical entities. Usually, biological drugs are complex protein products of living tissues, supposed to be identical to human molecules. Accordingly, it is very difficult to copy them in different laboratories. Biopharmaceuticals are the most complex biological drugs. They are produced by recombinant DNA technology, which is a very expensive and time consuming process. Biotech companies have a unique position in the market due to the cost of their products and potential earnings (see below).

A small number of biotech drugs may be copied or produced by other pharmaceutical companies. These copies are called “biologically similar drugs” or “biosimilars” in EU, “follow-on pharmaceuticals” in the USA and Japan, “subsequent entry biologics” in Canada and “biocomparables” in Mexico. Copies are never completely identical to the original (“twins but not clones”), so it is necessary to test them in clinical studies before the approval. This process is much more complicated than making a copy of the simple chemical drugs. Cost of clinical trials of biosimilars is high, and they may last more than a decade.

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3. The cost of biopharmaceutical research and development

The real cost of drug research and development (R&D) seems to be a controversial issue. For example, DiMasi et al. estimated that total cost of R&D of a new drug could exceed 800 million US dollars, which was two to four times higher than in other reports on that matter (DiMasi et al. 2003: 151). Their publication was based on confidential reports from pharmaceutical companies. New estimates were even higher, reaching 1,8 billion of US dollars per new drug (Light and Warburton 2005: 1030; Paul and Mytelka 2010: 203). The annual raise in R&D costs per approved biopharmaceutical molecule has reached 7% (Scherer 2011). It seems that

³ Drug patent protection in the U.S. lasts 20 years. However, pharmaceutical companies apply for patent protection before the drug is clinically tested and before it reaches the market. Actually, the real patent protects the first manufacturer of the drug between 8 to 10 years. When the patent expires, it is possible to make and sell copies of the original drug (originator brand) called generic drugs (short: generics). Their production is much cheaper, and the manufacturer is only required to confirm that generics contain the same active ingredients as the original/reference drug. In addition, generics should be tested for bioequivalence, i.e. the same part/percent of the dose administered should reach the target tissue compared to the reference drug.

pharmaceutical companies tend to exaggerate the total cost of drug R&D in order to justify their products' high prices. Such a trend is mainly due to rapidly increasing number of clinical trials of new drugs. The clinical R&D cost has increased more than fifty times during last 50 years (Scherer 2011)! In particular, it has become more difficult for pharmaceutical companies to prove that their products are better than those already on the market, not just due to tougher regulation/standards.

52 The second parameter that should be taken into account is the relative market share of biotech companies. According to Cavalla and Minhas, the biotech sector is under constant pressure to develop more biopharmaceuticals due to their economic shortcomings (Cavalla and Minhas 2010: 230). Namely, they are permanently between the "Scilla" of the highest expectations/future promise and potential (indicated by "price/earnings ratio") and the "Charybdis" of the lowest current earnings (indicated by "return on capital") compared to large pharma and generic pharmaceutical companies. There are different implications of such a trend: increasing use of non-human primates in preclinical biopharmaceutical drug development, changes in legislation that would abbreviate approval pathway for biosimilars, safety concerns regarding biopharmaceutical drug development and use, clinical trials of anticancer biotech drugs etc.

4. "Of mice and men": preclinical evaluation of biopharmaceuticals

Use of non-human primates (NHPs) in preclinical development of biopharmaceuticals raises public concerns. There is a long-term debate on that matter and a single conclusion could not be reached (see Nuffield Council on Bioethics conclusions on animal experimentation) (Perry 2007: 42). Animal liberation associations strongly oppose the use of NHPs in drug R&D, while pharmaceutical companies even argue that some NHPs could be found mainly in their breeding establishments, but not in the wild; also, they state that NHPs welfare is not significantly impaired in such establishments. In addition, replacement of NHPs with lower species is in agreement with 3R principles (Russell and Birch 1959; Todorović and Vučinić 2010), but neuroscientists state that their investigation is not possible without *in vivo* models close to humans (Abbott 2010: 964). Finally, experiments in NHPs are still considered to be "necessary in scientific procedures" in the Directive 2010/63/EU preamble (paragraph 17). An unresolved question is whether it is morally "worse" to use NHPs instead of lower species, e.g. dogs or mice, because there is a human prejudice for species physically more like ourselves. In other words, whether our lack of understanding of the mental lives of animals that are different from us could influence our decision regarding *in vivo* experiments. Number of NHPs used in biopharmaceutical drug development could be reduced in different ways: for example, refinement of experimental

design, and replacement of NHPs with lower species (e.g. transgenic mice) or the appropriate validated alternatives. However, such *in vivo* models are still inevitable in preclinical immunogenicity testing of new biopharmaceuticals. According to Chapman et al., NHPs still remain the only relevant species for preclinical safety testing of monoclonal antibodies (mAbs), and there is an increasing number of mAbs entering clinical trials (Chapman et al. 2009: 505). Accordingly, the trend of use of NHPs in preclinical testing of those biopharmaceuticals is actually increasing. The most important argument for and against the use of NHPs in preclinical drug testing is the same: they are close to humans. However, Baily opposes the use of NHPs in drug R&D as an “irrelevant, unnecessary, even hazardous to human health” having “little or no predictive value or application to human medicine” (Baily 2005: 235).

5. Legislation regarding biopharmaceutical medicine

Another controversial bioethics issues regarding biopharmaceuticals are changes in legislation that shorten approval pathways for biosimilars (generic versions of biopharmaceutics). Until recently, biosimilars were expected to pass more extensive (and more expensive) preclinical and clinical testing than their chemical counterparts. The first drug that was approved in the EU in accordance with the Directives 2001/83/EC and 2004/27/EC after such a complex procedure was Omnitrope[®], Sandoz. Recent changes in EU and US legislation have removed barriers for more rapid approval of biosimilars. It could significantly reduce the cost of treatment with biopharmaceutical drugs and decrease inequity in access to those highly efficient medicines, especially in developing countries. However, there are significant concerns regarding new standards for the assessment of their safety and efficacy. For example a copy of filgrastim, biopharmaceutical drug that stimulates bone marrow cells, was tested only in healthy volunteers. In particular, the number of leukocytes in peripheral blood was only checked in those volunteers in order to test the efficacy of such a biosimilar, without confronting its clinical efficacy and safety with the original drug (Anonymous 2012: 686). Abbreviated clinical testing of biosimilars in specific targeted small-scale clinical studies, and extrapolation of data from one indication to other indications for the same drug have replaced extensive testing. However, safety of biosimilar drugs should be separately tested for each indication, and such an extrapolation is not always adequate (Todorović et al. 2009: 467; Todorović and Prostran 2012: 133). The principle of justice (equal access to medicines) should not be in contradiction with another bioethical principle of non-maleficence (do not harm) in that particular case.

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6. Safety of biopharmaceuticals

Monitoring biopharmaceutical drug safety deserves special attention. It is not the sole duty of pharmaceutical companies (sponsors of clinical trials) to assess such

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a complex problem. The spontaneous reporting system of suspected adverse drug reactions involves both health professionals and patients. In particular, there is a need to recruit more volunteers from both cohorts to actively take part in such a monitoring, and to report their observations to national drug agencies (for example, Medicines and Medical Devices Agency of Serbia, ALIMS). Ethics in drug safety monitoring could be divided into two categories: individual and collective ethics (Palmer 1993: 219; Singer P 1981). Individual ethics assesses what is best for the present, individual patient; it is more suitable for rare (type B) adverse drug reactions and more common during early phases of clinical trials when drug safety is a primary endpoint. Individual ethics uses Bayesian statistical approach/ Bayesian probability theory in which sample data are real, and population data are only an abstraction. On the other hand, collective ethics analyzes what is best for the population of patients or society; it is more suitable for mild, reversible type A adverse drug reactions, and more common during late phases of clinical phases. Collective ethics uses traditional, frequentist statistical approach, which sees probability as the long-run expected frequency of occurrence (in other words, the frequentists believe that a population mean is real but unknown, and can be only estimated from the sample data) (Annis, internet). The main disadvantage of the spontaneous reporting system of adverse drug reactions is diffusion of responsibility (“no one is responsible”), which may lead to underreporting. It might be overcome in different ways; we can, for example disseminate information on drug safety, promote education in pharmacovigilance, increase motivation and strengthen the responsibility of individuals to participate in such a reporting system. In other words, we should try to overcome this “Bystander effect” of health professionals, i.e. to move “individual focus away from feeling uninspired by their diffusion of responsibility and towards individual responsibility being promoted in a way that makes them feel as though their combined efforts will make an effectual collective” (Beaker 2011: 1). In addition, lack of knowledge on drug safety and poor prescribing skills of young medical doctors should be taken into account (Harding 2010: 598).

7. Conclusion

In conclusion, biopharmaceuticals are not a Panacea, and their efficacy and safety should be carefully weighed against their cost. However, this is a not just a pharmacoeconomic issue. Widespread availability of biosimilars would enable more patients to be treated with these highly effective drugs, especially in developing countries, which is consistent with the bioethical principle of justice. Of course, it does not preclude improvement of standards in assessment of the safety of those complex agents.

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Bioetička pitanja u razvoju biofarmaceutika

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Apstrakt

Razvoj biofarmaceutika predstavlja izazov u bioetici. Za razliku od uobičajenih lekova male molekulske mase, biofarmaceutici su proteini kompleksne trodimenzionalne strukture koji se dobijaju tehnologijom rekombinantne DNK i tehnikom hibridoma. Imunogenost biofarmaceutika treba uvek proveriti u kliničkim studijama zbog male prediktivne prednosti pretkliničkih animalnih modela. Međutim, primati (izuzev čoveka) i transgeni sojevi miševa mogu se upotrebiti da bi se naznačili neki aspekti imunogenosti. Značajni napori su učinjeni u cilju smanjenja upotrebe primata u razvoju biofarmaceutika, npr. poboljšanja dizajna istraživanja i promene u zakonskoj regulativi. Osim toga, u ovoj oblasti su aktivne i pojedine ekspertske grupe (npr. NC3Rs, BioSafe i Biopharmaceutical Technical Group). Uprkos tome, postoji rastući trend upotrebe primata izuzev čoveka u pretkliničkom ispitivanju bezbednosti biofarmaceutika, posebno kada su u pitanju monoklonska antitela. Druga bioetička pitanja koja se mogu dovesti u vezu sa razvojem biofarmaceutika su odnos njihove cene i efikasnosti, procena bezbednosti u kliničkim uslovima, proizvodnja biološki sličnih lekova i upoređivanje njihove efikasnosti sa placebo u zemljama u kojima ne postoji namera o plasmanu. Upoznavanje humanog genoma otvorilo je mnoga bioetička pitanja. Razvoj biofarmaceutika je važno bioetičko pitanje iz više razloga. Ono povezuje sve aspekte savremene bioetike: biomedicinu (npr. klinička ispitivanja na vulnerabilnim ispitanicima), dobrobit životinja i najnovija dostignuća u biotehnologiji. Posebno, razvoj biofarmaceutika je izazov kada je u pitanju lečenje retkih bolesti.

Ključne reči bioetika, biofarmaceutici, razvoj lekova, imunogenost, dobrobit životinja, primati izuzev čoveka.